Innate Immune Mechanisms: Nonself Recognition

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Secondary article

Article Contents

The innate immune system contains a range of cell-bound and soluble proteins which eliminate pathogens by recognizing unique molecular patterns expressed by microorganisms, but not by host cells. Alternatively, host cells express proteins that protect them from attack by the alternative pathway of complement activation whereas foreign organisms lack these protective proteins and are, therefore, susceptible to complement attack.

Introduction

Most multicellular organisms possess some form of innate immunity to life-threatening pathogens. In contrast, the adaptive immune system is restricted to vertebrates. In fact, it has been estimated that 98.6% of multicellular animal species are unable to produce an adaptive immune response to a pathogen (Parish and O'Neill, 1997). As a result of this deficiency many species have evolved highly sophisticated mechanisms of innate immunity which have the ability to discriminate between self and nonself.

In the innate immune system, two basic mechanisms are used to discriminate self cells from foreign organisms. The first involves an array of cell-bound and soluble molecules that have evolved to recognize 'pathogen-associated molecular patterns' and have minimal cross-reactivity with self cells (Medzhitov and Janeway, 1997). For example, many of these molecules recognize unique carbohydrate structures associated with the cell walls of bacteria, yeast and protozoa which are essential for the survival of the organisms. The second mechanism of self–nonself discrimination does not require recognition of pathogen-specific molecular patterns but involves protecting self cells from the destructive effects of innate immunity. The best defined example of this process is the alternative pathway of complement activation in which a range of host proteins prevents complement activation on the surface of self cells. In contrast, the surfaces of foreign organisms do not possess such inhibitory proteins and, consequently, the organisms are lysed by the lytic pathway of complement activation. In a similar manner natural killer cells probably discriminate between infected and uninfected self cells, although this system is less well understood.

Recognition by Phagocytic Cells

Phagocytic cells are generally regarded as the major effector cells in innate immune responses. Tissue-associated phagocytes, usually termed macrophages, represent a preexisting first line of defence against invading microorganisms. They are strategically placed beneath epithelial surfaces to guard against the entry of foreign organisms from the external environment. Pathogen recognition by macrophages results in both pathogen destruction and the recruitment of additional phagocytic cells from the circulation to the site of invasion. It would be anticipated, therefore, that phagocytic cells should express an array of pathogen-specific receptors on their surface. In fact, a number of receptors have been identified on the surface of mammalian macrophages that have been implicated in the recognition of pathogen-associated molecular patterns. These receptors can be subdivided into four protein families, based on their molecular structure: C-type lectins, scavenger receptors, leucine-rich proteins and integrins (**Table 1**). In each case the receptors aid phagocytosis and elimination of ligand-bearing molecules or organisms, with macrophage activation also occurring as a consequence of receptor engagement. An important feature of macrophage activation is the secretion of a range of low molecular weight mediators and cytokines such as interleukin (IL) 1, IL-6, IL-8 and tumour necrosis factor (TNF). These mediators and cytokines can act locally to induce an inflammatory response, a key element of both innate and adaptive immune responses to pathogens.

C-type lectins

Each family of receptors has unique features that allow them to interact preferentially with foreign organisms. In this regard the C-type lectins are a particularly important

Table 1 Microbial-specific receptors on phagocytic cells

Protein family	Receptor	Microbial ligand	Primary function
C-type lectin	Mannose receptor	Terminal mannose	Phagocytosis, macrophage activation
	DEC 205 (mannose receptor related)	Carbohydrates (?)	Phagocytosis
	Galactose-specific lectin	Terminal galactose, *N*-acetylgalactosamine	Phagocytosis by hepatocytes
Scavenger receptor	Macrophage scavenger receptors type I and II	Anionic polymers	Phagocytosis, macrophage activation
	MARCO	Anionic polymers	?
Leucine-rich protein	CD14	Microbial LPS (via LPS binding protein)	Phagocytosis, macrophage activation
Integrin	CD11b/CD18 (Mac-1 or CR3)	β-Glucans, LPS	Cell activation, phagocytosis

·LPS, lipopolysaccharide. Based on data reviewed in Medzhitov and Janeway (1997) and Parish and O'Neill (1997).

family of recognition molecules in innate immunity as they have specificity for many of the unique polysaccharide structures incorporated in the cell walls of microorganisms. Furthermore, C-type lectins are not restricted to the surface of phagocytes, some existing as secreted molecules. Thus, owing to their complexity and importance, this class of recognition structures is discussed in detail in a separate section below.

Scavenger receptors

There are two important scavenger receptors on macrophages involved in innate immunity, type I and type II, which together are called macrophage scavenger receptor A (Kodama *et al*., 1996). These receptors have the ability to bind to negatively charged (anionic) polymers on the surface of microbes, such as the ubiquitous microbial-derived molecule, lipopolysaccharide (LPS). Interestingly the same scavenger receptors also play an important role in the recognition and elimination of senescent and apoptotic self cells, probably by interacting with negatively charged phospholipids that are displayed on the surface of dying cells. The macrophage scavenger receptor A is a trimolecular membrane protein with four, C-terminal, extracellular domains. Each molecule has three ligand-binding domains, which are cysteine-rich and are located at the C-terminal end of the molecule, with the ligand-binding region of the receptor being connected to the cell surface by a long fibrous stalk. Another scavenger receptor, termed the MARCO receptor, which is similar in molecular structure to macrophage scavenger receptor A, also has been described and is proposed to be involved in innate immunity although its functional significance is still unclear (**Table 1**).

CD14 and lipopolysaccharide-binding protein

CD14, a member of the leucine-rich glycoprotein family, is a glycosylphosphatidyl-inositol (GPI)-linked receptor on phagocytes that acts indirectly as a LPS receptor by recognizing complexes of LPS and a soluble, 65-kDa, LPS-binding protein present in plasma (Fenton and Golenbock, 1998). Thus the primary recognition molecule in this form of innate immunity is not the phagocyte receptor but the soluble plasma protein. In terms of self–nonself discrimination, the LPS-binding protein in plasma interacts with lipid A, a unique lipid structure expressed by bacterial LPS. Following interaction of the complex of LPS and LPS-binding protein with CD14, the LPS is transferred to CD14 which then mediates phagocyte internalization of the LPS. Also, it should be noted that a second accepted role of the LPS-binding protein in innate immunity is to shuttle LPS into high-density lipoprotein particles in plasma, a process that results in LPS neutralization.

Integrins

Integrins usually play an important role in cell migration and tissue integrity by acting as adhesion molecules in cell–cell and cell–matrix interactions. However, the myeloid-specific integrin CD11b/CD18, also known as Mac-1 and complement receptor 3 (CR3), is an exception. As well as behaving like a conventional integrin by interacting with fibrinogen and intercellular adhesion molecule 1 (ICAM-1), it has a binding site with specificity for microbial cell

wall polysaccharides such as yeast-derived β-glucans and bacterial LPS. Recent studies suggest that the sugar specificity of CD11b/CD18 is broader than originally thought, the receptor binding not only glucose-containing polysaccharides but also polymers containing mannose and *N*-acetylglucosamine. Furthermore, the sugar-binding region of the receptor is distinct from the domains of the molecule involved in binding other ligands such as C3 fragments, ICAM-1 and fibrinogen. Thus, in terms of ligand binding, CD11b/CD18 could be classified as a unique, calcium-independent, lectin with additional integrin-like properties.

Lectins

Lectins are carbohydrate-binding proteins other than enzymes and antibodies. All of the lectins that have been implicated in innate immunity, with the exception of CD11b/CD18, belong to the C-type lectin family. These lectins are characterized by calcium dependent carbohydrate binding and by the sharing of a common carbohydrate recognition domain (CRD) of 115–130 amino acids containing 14 invariant and 18 highly conserved amino acid residues. Lectins involved in innate immunity either function as cell surface receptors for microbial carbohydrates or exist as soluble proteins in tissue fluids. Each of these lectin classes is considered separately below.

Cell surface lectins

Table 1 lists three C-type lectins that can act as pathogen-specific receptors on phagocytic cells. There are a number of other C-type lectins that have been described on the surface of mammalian macrophages. However, most of these lectins have not been shown to be involved in pathogen recognition and, therefore, have been excluded from this discussion.

Mannose receptor

The most well-characterized cell surface lectin involved in innate immunity is the macrophage mannose receptor (Stahl and Ezekowitz, 1998). This receptor has the ability to recognize a remarkably wide range of microorganisms such as mycobacteria, Gram-negative and Gram-positive bacteria, yeasts, protozoa and viruses. How a single receptor can recognize such a diverse range of organisms without interacting with self structures is not fully understood, although recognition of carbohydrate patterns on the surface of microorganisms is clearly involved. An examination of the structure and carbohydrate specificity of the receptor has, however, provided some clues.

The mannose receptor is a single-chain molecule of 180 kDa, consisting of five domains, namely a short N-terminal cysteine-rich domain, a fibronectin type II domain, a region containing eight tandem CRDs, a transmembrane domain and a short cytoplasmic domain at the C-terminus (**Figure 1**). Each of the eight CRDs contains appropriate amino acids for carbohydrate recognition, although only two of the CRDs (CRD4 and CRD5) contain residues believed to be required for calcium binding, suggesting that these two domains constitute the major carbohydrate recognition region of the molecule. Although originally defined as a receptor for mannose, it is now clear that the molecule can interact with hexoses that have equatorially placed hydroxyl groups at carbons C3 and C4 (i.e. mannose, fucose, *N*-acetylglucosamine and glucose, but not galactose) with the receptor recognizing branched chain, rather than linear, oligosaccharides

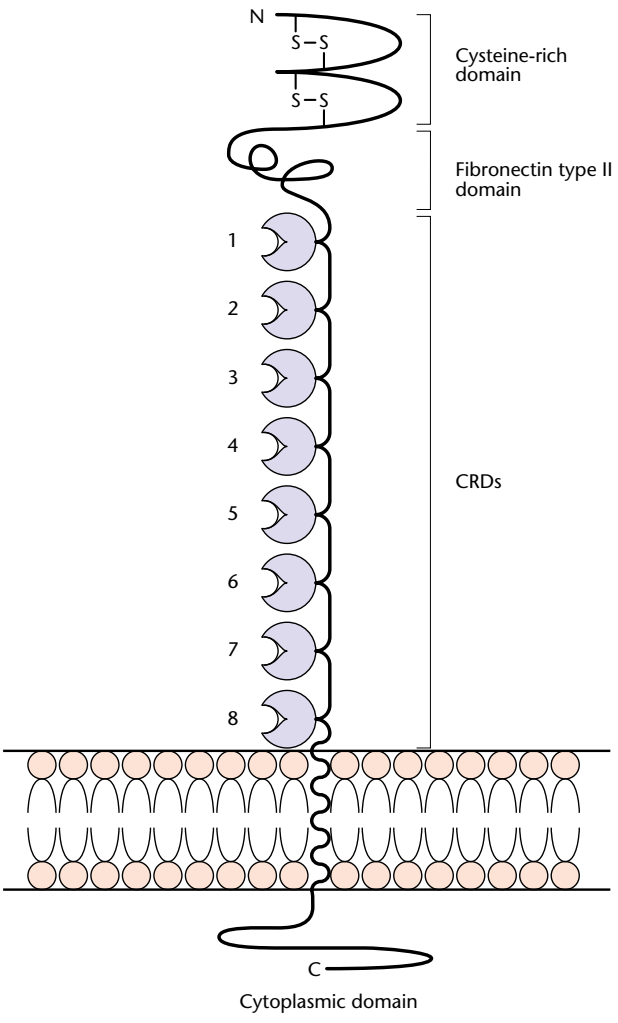

Figure 1 Structure of the mammalian macrophage mannose receptor. The molecule contains eight carbohydrate recognition domains (CRDs) arranged in tandem. Only CRD4 and CRD5 possess the appropriate structural features required for calcium-dependent carbohydrate binding. Although the CRDs are depicted in a linear array, the actual three-dimensional arrangement of the eight CRDs is not known.

containing the appropriate hexoses. However, the binding affinity of the functional CRDs is low, indicating that stable interaction of the receptor with a ligand requires the multivalent interaction of several, closely clustered, mannose receptors on the macrophage surface with multiple carbohydrate ligands. Based on these observations it appears that ligand geometry is the key element of self–nonself recognition by the mannose receptor, the molecule having evolved selectively to recognize repetitive carbohydrate structures on the surface of microorganisms.

Although originally thought to be a receptor restricted to tissue macrophages, it is now evident that the receptor can be expressed by many other cell types, such as some endothelial cells, some smooth muscle cells, and kidney mesangial cells. It seems likely that these expression patterns relate to other functions of the receptor not necessarily involved in innate immunity. For example, the receptor binds sulfated carbohydrates on certain hormones via a region distinct from the CRDs. Similarly, the cysteine-rich domain has been implicated in targeting soluble forms of the receptor to other cells of the lymphoid system. The latter function, in fact, may be an example of a linkage between the innate and adaptive immune systems. Thus, the mannose receptor resembles CD11a/CD18 in being involved in innate immunity as well as other, relatively unrelated, functions.

Following ligand engagement the mannose receptor activates an array of macrophage responses (**Table 1**), notably proinflammatory mediator and cytokine production, and the secretion of lysosomal enzymes into the surrounding environment. Cytokines, such as interferon γ and IL-4, also can influence the expression and functional properties of the mannose receptor on macrophages. Although receptor density is downregulated, the receptor becomes more effective at mediating phagocytosis, rather than endocytosis, of bound ligand. It should be emphasized that the transport of ligands via the endocytic pathway may be particularly important in allowing ligands to be processed appropriately for presentation to the adaptive immune system. This is another example of the way in which the mannose receptor, a pattern recognition receptor of the innate immune system, can facilitate activation of adaptive immune responses.

DEC 205

There are at least three other C-type lectins that have a domain structure very similar to that of the mannose receptor and have been classified as members of the 'multilectin mannose receptor family'. One of these molecules, DEC 205, a 205-kDa glycoprotein on the surface of macrophages and dendritic cells, is thought to act as an endocytic–phagocytic receptor for certain glycosylated molecules (**Table 1**). Whether the receptor contributes to innate immunity, however, is unclear as the emphasis so far has been on its role in enabling dendritic cells to internalize glycosylated antigens and present them to the adaptive immune system. Furthermore, sequence analysis of the 10 putative CRDs in DEC 205 has revealed that none contains the consensus amino acids required for carbohydrate or calcium binding. It appears likely, therefore, that carbohydrate recognition by this receptor may differ substantially from that by the mannose receptor and may even involve cooperative binding with another carbohydrate-binding receptor. The role, if any, of the other two members of the multilectin mannose receptor family in innate immunity remains to be established.

Galactose-specific lectin

One of the first mammalian lectins to be characterized was a receptor located on the sinusoidal membrane of hepatocytes which recognizes and eliminates asialoglycoproteins and effete cells from the circulation. The complex oligosaccharide side-chains carried by glycoproteins in mammalian plasma normally terminate in sialic acid residues. If terminal sialic acid is not attached, a subterminal galactose residue is exposed which is recognized by a galactose-specific C-type lectin in the liver, the asialoglycoprotein receptor. Initially it was thought that this galactose-specific receptor cleared ageing and inappropriately glycosylated self glycoproteins and cells from the circulation, analogous to the scavenger receptor's role in eliminating ageing and apoptotic self cells (Lodish, 1991). However, another potential function for this receptor is the recognition and clearance of bloodborne microorganisms, particularly enveloped viruses, which may express inappropriately glycosylated glycoproteins in their protein envelopes. Clearly this form of innate immunity cannot be classified as a first line of defence but could still play an important role in restricting the systemic spread of certain pathogens. It should be noted, however, that a role for this recognition system in microorganism clearance is still speculative, as hepatocytes may not possess the antimicrobial machinery required to destroy internalized microorganisms.

Soluble lectins

So far, all of the soluble lectins that have been demonstrated to play a role in mammalian innate immunity belong to the collectin family (Holmskov *et al.*, 1994). The name 'collectin' is derived from the fact that these molecules contain a collagen-like segment attached to a lectin domain. The best characterized collectin is human mannose-binding lectin (MBL), but at least three other collectins have been identified in humans and have been shown, to varying extents, to participate in pathogen recognition and elimination (**Table 2**). Additional collectins have been defined in other mammalian species, notably plasma conglutinin and CL-43 in cattle, but their human equivalents are not well characterized. Most collectins are

Table 2 Collectins: soluble lectins involved in pathogen recognition

Collectin	Major carbohydrate ligands	Major site of synthesis	Site of expression	Primary function
Mannose-binding lectin (MBL)	GlcAc > Fuc, Man, ManNAc	Hepatocytes	Plasma	Opsonization, complement activation (lectin pathway), phagocyte activation
Surfactant protein A (SP-A)	ManNAc>Fuc	Alveolar type II cells	Lung	Opsonization, neutralization
Surfactant protein D (SP-D)	Man, Glu > Gal	Alveolar type II cells	Lung	Opsonization (?), neutralization
P35	GlcNAc	Liver	Plasma	Opsonization

GlcNAc, *N*-acetylglucosamine; Fuc, fucose; Man, mannose; ManNAc, *N*-acetylmannosamine; Glu, glucose; Gal, galactose.

composed of several identical subunits, each subunit consisting of three, usually identical, polypeptide chains which interact to form a long, collagen-like, triple helical structure and three C-terminal CRDs (**Figure 2**). In fact, the C-terminal amino acids of each polypeptide chain fold up into independent globular CRDs.

Mannose-binding lectin

MBL, whose structure is schematically depicted in **Figure 2**, probably exists as a mixture of trimers, tetramers and pentamers of the basic collectin subunit, resulting in potentially 9 to 15 separate carbohydrate-binding sites per MBL molecule, depending on the extent of oligomerization. However, the degree of oligomerization is very much collectin dependent, with CL-43, for example, usually consisting of only one subunit. Structural studies of MBL have shown that the N-terminal portions of the collagenous regions of each subunit interact extensively, whereas the C-terminal regions are separate, resulting in a molecule with a bouquet-like appearance (**Figure 2**). This structure contrasts dramatically with the mannose receptor where the CRDs are arranged in a tandem fashion and are formed from a single polypeptide chain (compare **Figures 1** and **2**).

As with the mannose receptor, MBL has been shown to recognize a wide range of microorganisms, ranging from viruses such as human immunodeficiency virus (HIV) 1, HIV-2 and various strains of influenza A to many noncapsulated bacterial species and the parasitic protozoan *Leishmania*. The CRD of MBL interacts with a range of hexoses but with low affinity, the simultaneous binding of a number of CRDs being required to ensure high-affinity binding of a MBL molecule to a cell surface. It has been estimated that the three CRDs of each MBL subunit are separated by a distance of approximately 54 Å (5.4 nm). This separation distance makes it sterically impossible for a single mammalian high-mannose oligosaccharide to bind to more than one CRD and, therefore, owing to the low affinity of this monovalent interaction, recognition of self glycoproteins and self cell surfaces would be minimized. In contrast, the repeating carbohydrate structures on many microbial surfaces are at a much higher density and, consequently, would engage all three CRDs of MBL and bind with high avidity. As discussed above, a similar mechanism of self–nonself recognition probably occurs with the mannose receptor, although the details of this interaction are less well defined.

Once MBL has bound ligand with high avidity a number of functional consequences can occur. First, MBL can directly function as an opsonin as a number of MBL receptors have been identified on the surface of phagocytic cells. Second, and probably more importantly, MBL can activate the complement system by a novel lectin pathway of complement activation. The collagen-like region of MBL resembles C1q and complexes with a MBL-

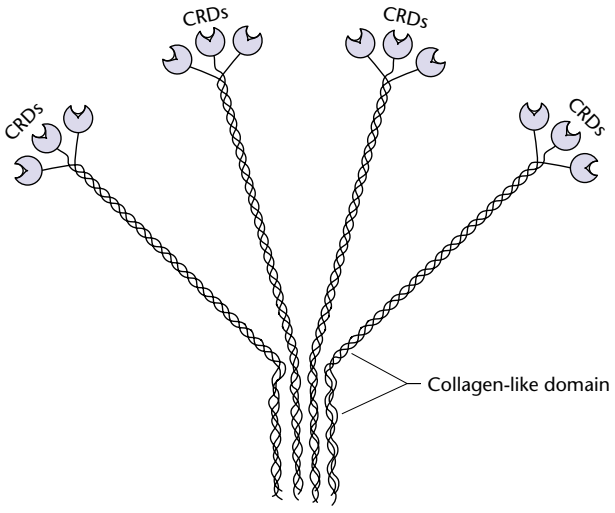

Figure 2 Structure of the human mannose-binding lectin, the best characterized collectin molecule. Note the bouquet-like structure of the molecule, a structure that has been validated by electron microscopy studies.

associated serine protease (MASP), which plays a critical role in initiating complement activation by a mechanism similar to the classical pathway. Obviously complement activation can result in lysis of the target organism but it can also, via massive C3b deposition on the microbial surface, dramatically augment the uptake of microorganisms by phagocytic cells. Finally, the interaction of MBL with phagocytic cells, either directly via MBL receptors or indirectly via complement receptors, can result in phagocyte activation.

Other collectins

The three other human collectins listed in **Table 2** are less well characterized than MBL. Two of these collectins, surfactant protein A (SP-A) and surfactant protein D (SP-D), are synthesized by the alveolar type II cells of the lung and are present in secretions associated with pulmonary surfaces. Each of these molecules exhibits slightly different carbohydrate-binding specificities when compared to MBL and to each other (**Table 2**). Structurally SP-A resembles MBL in forming a bouquet-like macromolecule, whereas SP-D exists primarily as monomers, although oligomers up to a tetramer may be found. Both molecules play an important role in acting as a first line of defence against pathogens entering via pulmonary surfaces. They appear not to fix complement, like MBL, but can opsonize microorganisms for uptake by phagocytes via specific collectin receptors. They may also play an important role in neutralizing some pathogens, particularly viruses, by masking carbohydrate structures on the surface of pathogens that are required for the infection of host cells.

Recently another human plasma collectin, called P35 based on the 35-kDa subunit molecular weight of the molecule, was characterized (Matsushita *et al.*, 1996) (**Table 2**). P35 resembles MBL in amino acid sequence, carbohydrate specificity and functional properties although its relative importance, compared with MBL, in providing protection against pathogens remains to be determined.

Alternative Pathway of Complement Activation

Unlike the pattern recognition molecules, which rely on recognition of microorganisms for activation of innate immunity, the alternative pathway of complement activation does not depend on such a system of self–nonself discrimination. Instead, this system of pathogen destruction is regulated at the effector level such that self cells are protected from the effects of complement activation, whereas foreign cells are destroyed.

The salient features of the alternative pathway of complement activation which are involved in innate immunity are depicted in **Figure 3**. The third component of complement, C3, is continually being spontaneously activated at a low rate in plasma via a process called 'C3 tickover'. This tickover process results in the cleavage of C3 to C3b. Normally, most of the C3b is inactivated by hydrolysis, but some C3b molecules can become covalently attached to the surface of host cells or pathogens via a highly reactive thioester group on C3b. Once bound to a surface, C3b can form a complex with factor B, the factor B then being cleaved by factor D into Ba and Bb fragments. The Bb fragment remains associated with the C3b to form a C3bBb complex, a potent protease complex (C3 convertase) which cleaves C3 to generate more C3b. This complex can be further stabilized by properdin (factor P) to produce a long-lasting convertase capable of cleaving many C3 molecules. If the C3bBb convertase is bound to the surface of a microorganism or foreign cell, huge numbers of C3b fragments are generated which decorate the surrounding cell surface. For example, it has been estimated that within 5 min of being exposed to serum a foreign red blood cell can be coated with as many as 2×10^6 C3b fragments. The deposited C3b can act as an opsonin for clearance of the foreign particle or can trigger activation of the terminal pathway of complement, which results in assembly of the membrane attack complex and resultant cell lysis (**Figure 3**).

On the other hand, if the C3b fragments initially interact with host cells, they are rapidly inactivated by a number of proteins on the surface of self cells, such as complement receptor 1 (CR1), decay-accelerating factor (DAF), and membrane cofactor of proteolysis (MCF), in collaboration with the soluble plasma proteins, factor H and factor I. This complex array of complement regulatory proteins protects self cells from inadvertent opsonization and lysis

by the complement system and represents a powerful form of self–nonself discrimination.

Acute-phase Proteins

Following infection or tissue injury the concentration of a number of liver-derived plasma proteins increases substantially. This phenomenon is one aspect of the 'acute phase response' and the proteins that behave in this manner are called acute-phase proteins/reactants (APPs) (Mortensen, 1993). The increased plasma concentration of the APPs is due to enhanced liver synthesis of these proteins, chiefly induced by inflammation-associated cytokines such as IL-1, IL-6 and TNF.

A number of proteins associated with innate immunity have been shown to be APPs. In particular, the plasma concentration of several pattern recognition proteins increases markedly during the acute-phase response, an effect that would be expected to enhance protection against invading microorganisms. The most notable of these is MBL and the LPS-binding protein whose plasma concentrations can increase several fold during the acute-phase response. However, one pattern recognition protein stands out as being massively increased during the acute-phase response, namely C-reactive protein (CRP) (Steel and Whitehead, 1994). Normally the plasma concentration of CRP is only 1 $\mu g\,mL^{-1}$ but can increase up to 1000-fold in the course of certain diseases.

Structurally CRP is a member of the pentraxin family of proteins, consisting of a characteristic pentameric structure of identical subunits. Functionally it is a classic pattern recognition protein, its major ligand being the phosphorylcholine expressed in the cell walls of certain microorganisms but not the phosphorylcholine present in the membranes of self cells. In terms of pathogen specificity it has been shown to opsonize organisms as diverse as bacteria, fungi and yeasts, with CRP being particularly effective against pneumococci, *Haemophilus inzfluenzae* and *Streptococcus pneumoniae*. CRP also has the ability, when bound to microorganisms, to activate the classical pathway of complement.

Another important feature of the acute-phase response is the increased liver synthesis of many complement components. The most important, in terms of the alternative pathway of complement activation and hence the innate immune response, are C3, C5, C9 and factor B. C3 is the critical initiating protein of the alternative pathway, factor B is an essential component of the alternative pathway C3 convertase (**Figure 3**), whereas C5 and C9 are key participants in the membrane attack complex that mediates cell lysis.

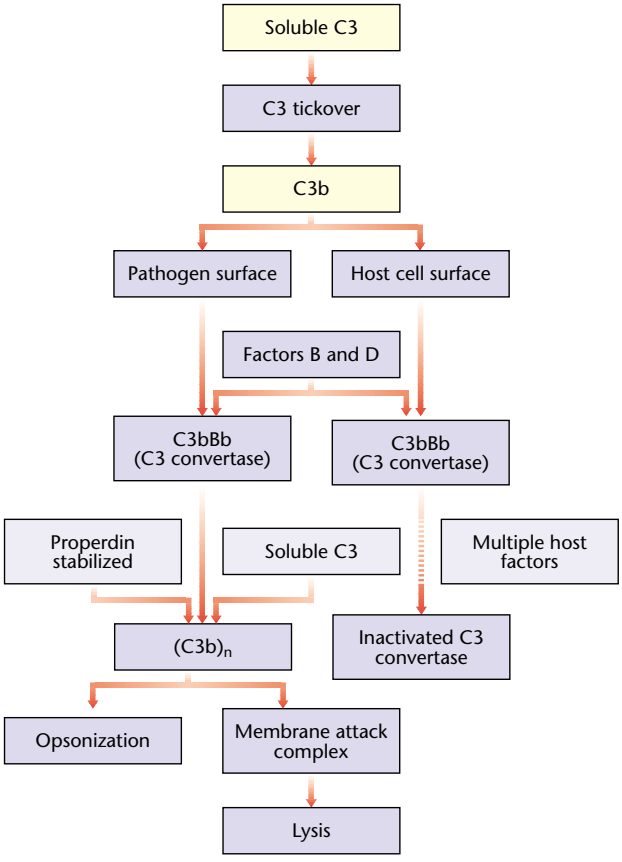

Figure 3 Self–nonself discrimination by the alternative pathway of complement. Fluid phase C3 is normally hydrolysed at a slow rate by the 'C3 tickover' process to generate C3b. The C3b possesses a highly reactive thioester group which can covalently attach some C3b molecules to the surface of both pathogens and self (host) cells. Following recruitment of factor B and the action of factor D, a C3 convertase (C3bBb) is formed consisting of a fragment of factor B (Bb) and C3b. On host cell surfaces this C3 convertase is rapidly inactivated by a number of host factors. In contrast, on the surface of microorganisms the C3 convertase is stabilized by properdin (factor P), is not inactivated by host factors, and generates massive numbers of C3b fragments. The C3b coats the surface of the microorganism and acts as an opsonin as well as initiating the formation of the membrane attack complex and eventual cell lysis.

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